III. Remarks

A. Status of the Application

Claims 35-37 are amended to address the §112, second paragraph, rejection, to clarify that the target receptor of Claim 35 is single-stranded, and to clarify that the target receptor of Claims 36 and 37 is double-stranded. Claim 38 is added and has support throughout the drawings and the specification. Claims 8 and 11 are amended to also be dependent upon Claim 38.

Claims 8-11 and 35-38 are pending.

B. Rejections of Claims 8-11 and 35-37 under 35 U.S.C. §112, First and Second Paragraphs

Office Action

Claims 8-11 and 35-37 were rejected in the Office Action for failing to comply with the written description requirement. Attention was directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428. The cited paragraph of the Office Action ends with a quote from *Lockwood*, 107 F.3d at 1572, "Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, not that which makes it obvious, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention."

At item 3. of the Office Action the independent Claims 35-37 are reproduced.

At item 4. of the Office Action, the pending claims are construed as being product claims and as encompassing virtually any nucleic acid.

At item 5. of the Office Action, Claim 35 is construed as encompassing nucleic acid that is bonded either indirectly or directly with the carrier particle, as encompassing nucleic acid in a double stranded or in a triplex structure, as encompassing rRNA, tRNA, and mRNA, and as encompassing both nucleic acids of known and unknown sequence.

At item 6. of the Office Action, Claims 36 and 37 are stated as construed as product claims.

At item 7. of the Office Action, Claims 35-37 are construed as requiring at least two labeling substances bound to different fractions of any number of target receptors and the labeled complex has a predetermined molar ratio of the types of labeled substances.

At item 8. of the Office Action, U.S. Patent 6,465,241 is cited as providing the axial rise per nucleotide in DNA and uses this information to state that the applicants' single stranded nucleic acid would have a length up to 30,303 bases.

At item 9. the Office Action states that the disclosure fails to provide a written description of a nucleic acid of 30,303 bases.

At item 10. the Office Action states that the disclosure fails to provide a Sequence Listing.

At item 11. the Office Action states that the failure to set forth any nucleic acids labeled with different labels in a predetermined molar ratio even when the nucleic acids have the same length and differ by but a single nucleotide does not reasonable suggest that applicant had possession of such a complex and that the absence of a description of such mandatory components fails to satisfy the written description requirement.

At items 12. and 13., the Office Action states that the nucleic acids as genes, tRNA, rRNA, or mRNA do not share the same structure function relationship and that such labels identify how they are to function, not what they are. Further, the Office Action states that the disclosure does not distinguish one tRNA, mRNA, etc. from another or a single nucleic acid in terms of what it encodes. The *Fiers v. Sugano* and *University of California v. Eli Lilly and Co* decisions are cited regarding conception of a substance. The Office Action states that the specification does provide literal support for use of the various terms, however the terms in combination with the figures do not rise to the level of an adequate written description.

At items 14. and 15., the Office Action states that the limitation of the length of nucleic acid found in the body of the disclosure can not be read into the claims.

At items 16 and 17, the Office Action states that determination of patentability of a product-by-process claim is based on the product.

At item 18. the Office Action cites the disclosure of O'Neill as containing a Sequence Listing.

At items 19-21 of the Office Action, the second usage of the word "of" is cited as creating indefiniteness to the claims.

Response

In contrast to the decision in the University of Rochester case, the presently pending claims are to a product that is described and enabled, not a product that is the result of a screening method that hasn't been described. The structures of the drawings and the specification clearly provide written description support for the claimed invention which speaks to properties of nucleic acids in general.

Regarding item 4. of the Office Action, the pending claims are product claims. Regarding the Office Action statement that the claims encompass virtually any nucleic acid, please note that the nucleic acid target receptors set forth in the claims have a length of up to 10 microns, and have specific ends thereof bonded to a carrier and/or a label. The cited Office Action statement is an incorrect construction of the claims as regards to length and other cited properties.

Regarding item 5. of the Office Action, Claim 35 sets forth a labeled complex that comprises (in part) single-stranded nucleic acid target receptors that are bonded to the carrier particle. The specification language with regard to the type of bonding is "including chemical and physical bonding." The claim

states that the single-stranded nucleic acid has two ends, one end is bonded to a carrier particle and the other end is bonded to a label. The statement of the Office Action is correct in that a second nucleic acid strand may be annealed to the claimed single-strand nucleic acid. However the Office Action is incorrect in that that second strand nucleic acid is not the claimed single-stranded nucleic acid since the second strand is not bound to the particle and not bound to the label. The Office Action's recitation of Claim 35 "as encompassing rRNA, tRNA, and mRNA" is correct if the rRNA, tRNA, or mRNA is "a single-stranded nucleic acid target receptor bonded at one end to a carrier particle and bonded at the other end to a label."

The sequence of the single-stranded nucleic acid target receptor need not be known. The present invention speaks to generic properties of nucleic acids that have been discussed previously during prosecution of this case. Further, a working example in the specification is not required for satisfying the written description requirement.

Regarding an "indirect linkage" between a solid support and a polynucleotide, the definition of O'Neill (cited in the Office Action) at column 18 line 35 of an "indirect linkage" is where the linkage is through a specific binding pair such as biotin-avidin or antigen-hapten. The bonding between a polynucleotide and its complement is not included in O'Neill's examples of an "indirect linkage."

Regarding item 6. of the Office Action, Claims 36 and 37 are correctly construed as product claims.

Regarding item 7. of the Office Action, certain claim language is omitted from the Office Action description, for example: Claims 35-37 recite that the number and length of target receptors bonded to said carrier particle is such that energy movement among the labeled substances and occurrence of quenching are prevented, thereby enhancing consistent discrimination of emissions. Further, Claims 35-37 recite that the labeled complex has a "predetermined molar ratio of the types of labeled substances in all of said labeled substances of the carrier particle."

Regarding items 8. and 9. of the Office Action, the claimed length of target receptor is clearly set forth in the specification at page 8, line 28, to page 9, line 9, specifically at line 9. Said lines state:

> *..., the target receptor, ..., is formed in a slender shape ... . (page 9, line 3). The size of the "slender shape" is not expressly defined (page 9, line 5). ... For example, the form is as long as or sufficiently longer than the particle size (page 9, lines 7-8), for example, about 10 times as long as the particle size, for example, about 10μm (page 9, lines 8-9).*

The Office Action states a conversion of the 10 micron length to numbers of nucleotides and then rejected the application for lacking a written description of that number of nucleotides. Applicants believe this rejection is improper. There is clear written description for the length of the target receptor at pages 8 and 9 as cited above.

Regarding items 10. and 11., a Sequence Listing is not required unless nucleotide or amino acid sequences of a certain minimum length are cited in the patent application. Applicants submit that Fig. 3(c) provides nucleic acids labeled with different labels (circles and triangles) in a predetermined molar ratio (4:1) even when the nucleic acids have the same length and differ by but a single nucleotide (the PCR products are shown as having similar if not the same length). Possession of such a complex is further described in the description of Fig. 3 (the paragraph begins "As shown in FIG. 3) under the section entitled "BEST MODE FOR CARRYING OUT THE INVENTION."

Regarding items 12. and 13., the invention speaks to properties of nucleic acids that are common to all nucleic acids, that is, all nucleic acids have a 5' end, a 3' end and hybridize to their complementary sequence. Therefore, the particular nucleic acid sequence of a target receptor of the present invention is of no consequence to the invention. To limit the present invention to any particular nucleic acid would do injustice to what the inventors have invented. The claims specify that the nucleic acid molecules have ends, therefore the claimed nucleic acids are linear, and all nucleic acids are composed of a linear arrangement of known bases. The particular sequence of bases matters not for purposes of the present invention. For purposes of the invention, the nucleic acid simply needs to have an end that can be labeled and/or another end that can be bound to a carrier particle as set forth by the claims.

Regarding items 14. and 15., the length of nucleic acid is an element of the pending claims.

Regarding items 16. and 17., Applicants understand that determination of patentability of a product-by-process claim is based on the product.

Regarding item 18., the disclosure of O'Neill likely contains a Sequence Listing since it is requirement of the Patent Office to include a Sequence Listing in a patent application where nucleotide sequences are present in the disclosure.

Attachments A and B demonstrate knowledge prior to the priority filing date of the present application showing that gene substances and fluorescent substances can be combined and gene substances and particles can be combined.

The citation for Attachment A is "Biomagnetic Techniques in Molecular Biology," Technical Handbook, 3rd Edition, March 1998, DYNAL®, Oslo, Norway.

The citation for Attachment B is "Long-Range and Highly Sensitive DNase I Foot-printing by an Automated Infrared DNA Sequencer," BioTechniques 23:300-303, August 1997.

Regarding items 19. – 21. of the Office Action, the second usage of the word "of" is deleted.

Applicants respectfully request that the rejections of Claims 8-11 and 35-37 under 35 U.S.C. §112, first and second paragraphs, be withdrawn for the reasons cited herein.

C. Common Ownership of the Subject Matter of the Claims

The subject matter of the claims was commonly owned at the time any inventions covered therein were made.

D. Rejections of Claims 8-11 and 35-37 under 35 U.S.C. 102(a and e) as anticipated by or under 35 U.S.C. 103(a) as obvious over U.S. 6,124,092 (O'Neill *et al.*)

Office Action

The Office Action states that Claims 8-11 and 35-37 are rejected over O'Neill *et.al.* as anticipated or obvious as follows.

At item 28. of the Office Action, Claim 35 and claims dependent thereon are interpreted as encompassing nucleic acid that is bonded either indirectly or directly with the carrier particle and, in the context of indirect bonding, the single stranded nucleic acid could be bound through interaction with a second strand of nucleic acid.

At item 29. of the Office Action, O'Neill *et.al.* is cited as disclosing the immobilization of "recovery primers" and "recovery tags."

At item 30. of the Office Action, O'Neill *et.al.* is cited as disclosing a list of solid supports.

At item 31. of the Office Action, O'Neill *et.al.* is cited as disclosing that primers can be labeled differently or that differently labeled chain terminating nucleotides can be added to a primer extension product.

At item 32. of the Office Action, O'Neill *et.al.* is cited as disclosing a single stranded nucleic acid that is bound to a solid support at one end and has a label at the other end meets the limitation that the immobilized nucleic acids can be tens of thousands of nucleotides long.

At item 33. of the Office Action, O'Neill *et.al.* is cited as disclosing nucleic acids present in a predetermined molar ratio by use of known concentrations of reactants in PCR.

At item 34. of the Office Action, O'Neill *et.al.* is cited as rendering obvious a compound comprising nucleic acids immobilized to a carrier where the nucleic acids are of a predetermined sequence, are labeled at the end opposite to that bound to the carrier, and are present in a predetermined molar ratio.

At items 36. and 37., the Office Action states an interpretation of both direct and indirect bonding of a single stranded nucleic acid to a carrier particle.

At items 38. and 39., the Office Action states that primer extension products are used in subsequent rounds of amplification and what constitutes a second single strand in one round of amplification can and does serve as the first single strand in the subsequent round of amplification..

At items 40. and 41. the Office Action states that O'Neill teaches amplification using labeled primers where the different primers in a multiplex reaction are labeled differently.

Response

The PTO provides in MPEP §2131 that:

"[t]o anticipate a claim, the reference must teach every element of the claim."

Therefore, to support this rejection with respect to each of Claims 35, 36 and 37, the O'Neill *et al.* patent must contain all of the above-claimed elements of each of the claims.

35 U.S.C. §103(a) provides that:

"[a] patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains ... (emphasis added)"

Thus, when evaluating a claim for determining obviousness, all limitations of the claim must be evaluated.

Claims 35, 37, and claims dependent thereon where the strand that is bound to the carrier is also bound to the label:

Independent Claims 35 and 37 are not anticipated or rendered obvious by O'Neill *et al.*(O'Neill) for the following reasons.

The bonding of the single-stranded nucleic acid target receptor (Claim 35) and the bonding of the first strand of a double-stranded nucleic acid target receptor (Claim 37) to the carrier particle may be by bonding such as chemical or physical bonding (the specification language is "including chemical and physical bonding"). However, the Office Action fails to recognize a limitation of the Claims 35 and 37 that states that that strand that is bound to the carrier also is bound to the label.

O'Neill's strand that is bound to the particle (the recovery tag binding compound) does not carry a label. O'Neill does not teach or suggest a recovery tag binding compound that is bound, within the same nucleic acid strand, to a label and to a solid support. O'Neill's label is bound to the primer or is part of the primer extension reaction and is always then part of the strand that is complementary to the immobilized recovery tag binding compound. Therefore, O'Neill *et al.* do not teach or suggest the subject matter claimed in Claims 35 or 37.

O'Neill at column 17, lines 9-19, sets forth beads with labels. O'Neill does not set forth recovery tag binding compounds that carry a label.

Regarding an "indirect linkage" between a solid support and a polynucleotide, the definition of O'Neill at column 18 line 35 of an "indirect linkage" is where linkage is through a specific binding pair such as biotin-avidin or antigen-hapten. The bonding between a polynucleotide and its complement is not included in O'Neill's examples of an "indirect linkage."

Since O'Neill does not teach a single-stranded nucleic acid target receptor (Claim 35) or a first strand of a double-stranded nucleic acid target receptor (Claim 37) as bonded to the carrier particle and to a label, O'Neill clearly fails to teach such receptors bound to a first and a second type of label. Even further, O'Neill clearly fails to teach such receptors bound to a particle and a first and second type of label wherein each label is bonded to a fraction of the number of target receptors, thereby forming a predetermined molar ratio of the types of labels in all of said labels of the carrier particle.

The Office Action is incorrect in stating that O'Neill meets the limitation that the nucleic acids are present in a predetermined molar ratio. Please note the claim language that states that the types of labeled substances in all said labeled substances of the carrier particle are in a predetermined molar ratio.

Claim 36 and claims dependent thereon where the first end of the first strand is bonded to the carrier and the second end of the second strand is bonded to the label.

O'Neill's labeled primers are on the wrong end of the annealed strand (strand not bonded to the solid support) to anticipate or make obvious Claim 36. As shown in Fig. 3A-3C of O'Neill, the Y, G, C, and M labels are on the end of the annealed strand closest to the solid support. In contrast, Claim 36 states that the first end of the first strand is bonded to the carrier and the second end of the second strand is bonded to the label. Therefore, O'Neill does not anticipate, teach, suggest, or render obvious the subject matter of Claim 36 as O'Neill relates to labeled primers.

Claim 35, 36, 37, and claims dependent thereon

The molar ratio of O'Neill's chain terminating nucleotide labels depends upon the base content of the strand being sequenced, the kinetics of incorporation of the labeled terminator and is not predictable from a known or an unknown sequence. Since the incorporation of the chain terminators is set up to provide a nested set of fragments of varying length, it is not possible to know how many fragments will be generated with a terminator at a particular location. Therefore, even in a situation where the sequence of a polynucleotide is known, one cannot simply count the number of A's, C's, G's, and T's and predetermine that the molar ratio of a G label to T label, for example, will be a certain value since the terminator reactions may incorporate certain chain terminating labels much more readily at a particular location thereby favoring the amount of that label in any predicted ratio.

In contrast, an element of Claims 35, 36, and 37 is a labeled complex having a predetermined molar ratio of the types of labeled substances in all said labeled substances of the carrier particle. Such a predetermined ratio is provided in the examples of the specification, for example, FIG. 5 provides a labeled complex 33 having label 13 and label 15 where the ratio of label 13 : label 15 is 4:1; and a labeled complex 34 having the same circle and triangle depictions for the labels and, in this case, the labels are in a 1:4 ratio.

As further evidence that O'Neill's labels are not the same as the claimed labeled substances, O'Neill states at column 12, beginning at line 7 that multiple fluorescent labels may be used in conjunction with one another so as provide for resonance energy transfer between fluorescent labels in order to obtain the desired spectral characteristics.

In contrast, Claims 35, 36, and 37 state that energy movement among the labeled substances and occurrence of quenching are prevented, thereby enhancing consistent discrimination of emissions. Therefore, the O'Neill reference teaches away from the invention as claimed by Claims 35, 36, and 37.

Please note that Claims 35, 36 and 37 recite that the types of labeled substances have a predetermined molar ratio. Here, the term "labeled substances" does not mean nucleic acids as the Office Action indicates, but means substances for labeling such as fluorescent substances or chemical luminescent substances.

Please note that the claims of the present invention do not recite that the nucleic acids immobilized to a carrier are present in predetermined molar ratio. The claims recite that a labeled complex has a predetermined molar ratio of the types of labeled substances in all said labeled substances of the carrier particle. Here, the term "labeled substances" does not mean nucleic acids as the Office Action indicates, but means substances for labeling such as those described at page 5 of the specification.

Further, in the present invention, there are at least two types of labeled substances bonded to a fraction of the number of target receptors, thereby forming a labeled complex having a predetermined molar ratio of the types of labeled substances, in all said labeled substances of the carrier particles.

In contrast thereto, in O'Neil, there is no description that two types of the tags are used for identifying a carrier from many other carriers by predetermining the molar ratio of the types in all the tags of the carrier.

Because O'Neil discloses a method of using only one carrier (solid support) using many distinguishable locations on the carrier, and using tags for identifying immobilized substances, as shown in abstract of O'Neil "The recovery tag binding compounds are immobilized on the solid support in an addressable manner, i.e. the recovery tag binding compounds have distinct locations on the solid support", and hence there is no motivation to identify the carrier from many other carriers and to take the trouble to distribute the recovery tag to each location on the carrier according to predetermined molar ratio of the types of the tags in all the tags of the carrier, for identifying the immobilized substances to the carrier.

In O'Neil where only a single carrier is used, if the molar ratio of the tags in the carrier were predetermined beforehand as the examiner alleges, it follows that the results of the assay are predetermined before assay. One cannot call such a process that the result is predetermined beforehand, an assay, and cannot use such a process for assay. Therefore, in O'Neil, the molar ratio of the tags cannot be predetermined beforehand.

Further, with O'Neill, the recovery tag (or recovery tag binding compounds, correspond to receptor of the present invention) is distinguished by a solid state itself (namely, locations thereon) or by bead itself (which is distinguished from one another by color-coding etc.) or by distinctive fluorescent label itself which directly fixed to receptors and distinguishes each recovery tag or by label directly fixed on a bead which distinguishes each bead, as shown in column 11, lines 10 to 14 and lines 15 to 25, column 16, lines 46 to 58, column 17, lines 10 to 19 of the O'Neill. Therefore, with O'Neill, any combinations of two or three means selected from a group of a solid state, beads and distinctive fluorescent labels fixed to receptor, are not used for identifying receptors. Hence, O'Neill does not teach or suggest a recovery tag binding compound that is bound, within the same nucleic acid strand, to a label and to a solid support. O'Neill's label is bound to the primer or is part of the primer extension reaction and is always then part of the strand that is complementary to the immobilized recovery tag binding compound and then is bound on the wrong end of the annealed strand.

In contrast thereto, with the present invention, the receptors are not distinguished by beads per se nor by a solid state per se (namely, locations thereon) nor by labeled substances directly fixed to the receptors per se nor by labeled substances directly fixed to the beads, but the receptors are distinguished by using beads and labeled substances fixed to the receptors in such a manner that cannot respectively distinguish the receptors but can cooperatively distinguish the receptors. Namely labeled substances fixed to the receptors do not distinguish each receptor respectively, but distinguish all receptors fixed to a bead from other receptors fixed to other beads. Hence, with the present invention, a fraction of the number of target receptors at the second end of each receptor bond to at least a first type or a second type of labeled substance, thereby forms a labeled complex having a predetermined molar ratio of the types of labeled substances, in all said labeled substances of the carrier particle.

Due to this distinction, with the present invention, many kinds of carrier particles can be identified by using at least two types of labeled substances.

Further, with the present invention, since labeled terminator sequencing or sequence information need not be obtained or various kinds of beads need not be prepared, or various kinds of receptors need not be delivered into locations on a solid support, labeling can be obtained easily by controlling molar ratios of first types and second types of labeled substances fixed thereto in all said labeled substances of the same kind of beads.

Further, according to the present invention as shown in specification of the present application, since the target receptors themselves bond to the labeled substances, the presence of labeled substances does not deteriorate the capture capacity of the target receptor and satisfy the development of the capture capacity and ability of identification. Further, in comparison with the case where the labeled substances directly bonded to the carrier surface, distance or interval between the labeled substances can be

enhanced, and energy movement and occurrence of quenching among the labeled substances are prevented and stable discrimination can be carried out.

In regard to Paragraph 33 and 34, the nucleic acids of the present invention may have a known or an unknown sequence. The present invention can use unknown nucleic acids for determining the structure of the unknown nucleic acids.

In summary, the rejections based on 35 U.S.C. §102(a and e) cannot be supported by O'Neill as applied to Claims 35, 36 or 37. Since the present invention has such remarkable advantages, Applicants submit the independent claims 35-38 and dependent clams 8 to 11 which depend thereon are patentable over the cited reference under 35 USC §103(a). As a result, the Patent Office's burden of factually supporting a prima facie case of obviousness clearly cannot be met with respect to Claims 35, 36 and 37, and a rejection under 35 U.S.C. §103(a) is not applicable.

Dependent Claims 8-11 depend from, and further limit, independent Claims 35, 36 and 37 in a patentable sense and therefore are allowable as well. In view of all of the above, the allowance of Claims 8-11, 35, 36 and 37 is respectfully requested.

E. Added Claim 38

With respect to added Claim 38, O'Neill does not anticipate or render obvious a mixture of labeled complexes for the reasons set forth under D. above and for the reason that O'Neill does not teach or suggest an embodiment where the predetermined molar ratio of the types of labeled substances for a first labeled complex is different than the predetermined molar ratio of the types of labeled substances for the second labeled complex thereby providing for discrimination of emissions of the first complex and the second complex.

Applicants respectfully submit that Claim 38 is patentable over O'Neill.

F. Conclusion

It is believed that all matters set forth in the Office Action have been addressed. Further reconsideration and an early indication of the allowability of the pending claims are respectfully requested. Should the Examiner believe that an interview with Applicant's undersigned agent would expedite consideration of the pending claims, the Examiner is invited to call the undersigned agent at 512.867.8528.

Respectfully submitted,

Gloria L. Norberg

Dated: April 8, 2005

Gloria L. Norberg
Registration No. 36,706

HAYNES AND BOONE, LLP
901 Main Street - Suite 3100
Dallas, Texas 75202-3789
Telephone: (512) 867-8400
Facsimile: (214) 200-0853
ipdocketing@haynesboone.com